The patient with heart failure in the face of the coronavirus disease 2019 pandemic

An expert opinion of the Heart Failure Working Group of the Polish Cardiac Society

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ABSTRACT
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a new coronavirus that induces acute respiratory failure among other conditions, is the cause of the rapidly spreading coronavirus disease 2019 (COVID-19), affecting thousands of people around the world. The present expert opinion is a synthetic summary of the current knowledge on the various aspects of heart failure in patients with COVID-19. The aim of the paper was to provide clinicians with necessary information useful in daily clinical practice.

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Introduction **Epidemiology of severe acute respiratory syndrome coronavirus 2 infection** At the end of 2019, a new virus, known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), caused an epidemic of acute respiratory disease in Wuhan, China.[1] The World Health Organization (WHO) called this condition coronavirus disease 2019 (COVID-19). By the time this position statement was submitted, COVID-19 has become a pandemic and is affecting more and more people in the world and in Poland (current data are available at: https://www.worldometers.info/coronavirus/#countries). Both the WHO and Centers for Disease Control and Prevention have issued preliminary guidelines for infection control, screening, and diagnosis in the general population. However, the existing guidelines are incomplete regarding data on the course of COVID-19 in patients with cardiovascular disease, including heart failure (HF).

Organization of care for patients with coronavirus disease 2019 in Poland To prevent the spread of the epidemic, on March 14, 2020, Poland introduced the state of epidemic emergency in connection with SARS-CoV-2 infection, followed by the state of the epidemic since March 20, 2020. This made it possible to take a set of preventive antiepidemic actions, as specified in a legislative act, to minimize the effects of the epidemic.

From March 16, 2020, 19 hospitals have been transformed into infectious disease hospitals that admit only patients with SARS-CoV-2 infection. At least 10% of the beds in such a hospital should be dedicated to respiratory therapy. These are multispecialty hospitals so that they can treat comorbidities in addition to

infections. Due to the growing number of patients with SARS-CoV-2 infection, the launch of the so called second-line infectious disease hospitals is planned in the near future. At the same time, isolation facilities are being created, which can accommodate patients with COVID-19 with no or mild symptoms. Constantly updated information on the COVID-19 pandemic in Poland, along with a list of infectious disease hospitals, is available on the official website of the Ministry of Health (https://www.gov.pl/web/koronawirus).

In the context of the COVID-19 pandemic, the proper triage of patients before arriving at a healthcare facility is of particular importance. It seems that telemedicine should largely enable an effective control of the patient as well as quick decision-making on isolation or quarantine. Such an approach directly protects other patients, medical personnel, and the community against the risk of contact with an infected person. Communication using smartphones and computers with a webcam is available 24 hours a day, 7 days a week. It enables the assessment of infectious and respiratory symptoms. Moreover, healthcare professionals can obtain detailed information concerning travel, exposure, or contact with infected individuals. An optimal approach would be to include telemedicine systems in screening algorithms, hospital admission process, and quarantine surveillance.[2,3]

Myocardial and vascular damage in the course of severe acute respiratory syndrome coronavirus 2 infection The effect of SARS-CoV-2 on the human body is closely related to the membrane receptor angiotensin-converting enzyme 2 (ACE2) and the renin–angiotensin–aldosterone (RAA) system. The transmembrane serine protease TMPRSS2 aids active binding of viral envelope proteins to the host cell. The ACE2 expression was identified in the cells of numerous organs (eg, oral cavity, colon, stomach, and gallbladder), including also type II alveolar epithelial cells, and the lungs seem to be the main route of entry for SARS-CoV-2.[4] Moreover, the ACE2 expression was noted in vascular endothelial cells, cardiomyocytes, and the cells of other organs, including the kidneys, which increases the risk of multiple organ damage.[5] On contact with the virus, the ACE2 expression decreases, which leads to a local increase in angiotensin II levels (the main substrate for ACE2), thus promoting RAA system stimulation. The exact mechanism of myocardial and vascular damage due to SARS-CoV-2 infection is currently being studied, with a special emphasis on the endothelium.[6] Most of the available data were obtained during severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) epidemics. By analogy to SARS-CoV, which has a similar genome to that of SARS-CoV-2, it can be speculated that SARS-CoV-2 causes direct damage to cardiac muscle cells. A study conducted during the SARS epidemic in 2002 revealed that 35% of patients with acute respiratory distress syndrome (ARDS) had the SARS-CoV-positive genome in the heart.[7] Thus, the virus can cause direct damage to the heart or affect the cardiovascular system indirectly through systemic proinflammatory stimulation (cytokine storm: high levels of interleukins [IL-1β, IL-6] and interferon-γ as well as immune response dysregulation) or as a consequence of ARDS[8] (FIGURE 1). Chinese authors reported elevated troponin levels in 12% to 28% of patients with COVID-19.[9-11] The increase in troponin levels during hospitalization was significantly correlated with higher levels of N-terminal fragment of the prohormone brain natriuretic peptide (NT-proBNP) and C-reactive protein.[9] In addition, in patients who died during hospitalization, troponin and NT-proBNP levels increased significantly compared with admission values, while no significant dynamic changes were noted among those who survived to discharge.[9] Elevated troponin T and NT-proBNP levels, and especially their dynamic changes during hospitalization, proved to be a strong predictor of death in patients with COVID-19.[9]

High-risk patients **Patients at high risk for severe course of severe acute respiratory syndrome coronavirus 2 infection** Patients aged 60 years or older are at risk for a more severe course of SARS-CoV-2 infection than children, who are at lower risk of infection and, if infected, may be mildly symptomatic or asymptomatic.[12] Compared with patients aged 30 to 59 years, those younger than 30 years and older than 59 years were 0.6 (0.3–1.1) and 5.1 (4.2–6.1) times, respectively, more likely to die after developing symptoms.[13] The risk of symptomatic infection increased with age (approximately 4% per year in adults aged 30 to 60 years).[13]

The severe course of SARS-CoV-2 infection is becoming a serious issue in the context of HF and its increasing incidence due to population aging, among other factors. Population aging is also associated with the presence of comorbidities, estimated to affect 63% of individuals aged above 65 years and particularly common among patients with HF.[14]

Another important issue in the setting of HF is the chronic and debilitating course of the disease that affects not only the heart but also other organs. Available data show that populations with increased susceptibility to a more severe course include patients with cardiovascular disease (mortality risk estimated at about 10%) and elderly individuals, particularly those above 80 years (also reported to have high mortality rates). This indicates that patients with HF should be considered at high risk for severe SARS-CoV-2 infection and should be carefully monitored for any developing symptoms.

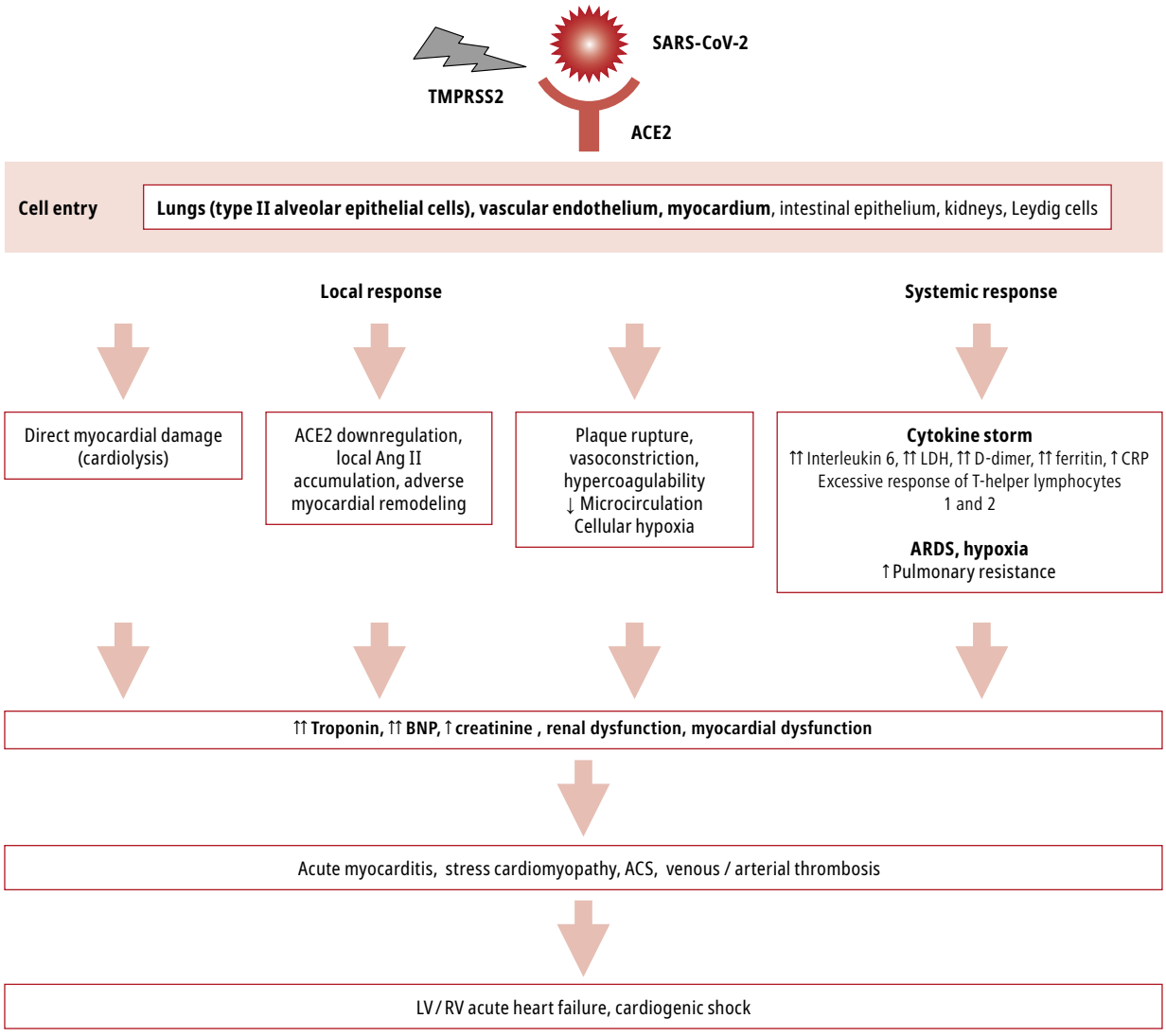

FIGURE 1 Postulated mechanisms of acute cardiovascular injury caused by severe acute respiratory syndrome coronavirus 2
↑ – moderate elevation
↑↑ – severe elevation
↓ – moderate reduction
↓↓ – severe reduction
Abbreviations: ACE2, angiotensin-converting enzyme 2; ACS, acute coronary syndrome; ARDS, acute respiratory distress syndrome; Ang II, angiotensin II; BNP, brain natriuretic peptide; CRP, C-reactive protein; LDH, lactate dehydrogenase; LV / RV, left ventricular / right ventricular; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TMPRSS2, transmembrane protease serine 2

The WHO has defined the profile of a patient at greater risk of COVID-19 by listing diseases and conditions associated with increased susceptibility. They include cardiovascular diseases (eg, hypertension, myocardial infarction, and stroke), diabetes, chronic respiratory diseases, and cancer.

Identification of patients at high risk for heart failure

There are scarce clinical data on de novo HF in patients with COVID-19, although the Chinese studies[9-11] indicate 2 possible scenarios: 1) development of HF in the acute stage of COVID-19, and 2) development of HF in COVID-19 survivors.

De novo heart failure in the acute stage of coronavirus disease 2019 Identification of patients who develop de novo HF in the acute stage of COVID-19 is a major challenge, as dyspnea is common to both conditions. De novo HF in the course of COVID-19 may be caused by acute myocardial inflammation, myocardial ischemia, Takotsubo syndrome, or arrhythmia. With severe respiratory infection / ARDS and hypoxia, due to COVID-19, this mechanism of injury appears to be important.[15] In a recent study including patients with COVID-19, Wang et al[10] reported acute cardiac injury in 7.2% of the cohort; shock, in 8.7%; and arrhythmia, in 16.7%. On the other hand, Huang et al [11] reported that 12% of patients developed acute cardiac injury with an increase in high-sensitivity troponin I levels and new abnormalities on electrocardiography and

echocardiography. In a study by Chen et al,[16] including 120 patients with COVID-19, elevated levels of NT-proBNP were noted in 27.5% of the population, and of cardiac troponin, in 10%. However, no data were reported on the percentage of patients who developed HF symptoms or on the time of symptom onset. Moreover, elevated troponin levels may be also related to multiple organ damage in the course of COVID-19. A rise in troponin levels was associated with a 4-fold higher risk of in-hospital mortality (hazard ratio, 4.26; 95% CI, 1.92–9.49).[17]

De novo HF may develop at different stages of COVID-19, depending on etiology. However, it most often occurs in the third stage of acute disease (FIGURE 2), which is characterized by multiorgan failure associated with an enhanced immune response, with the predominant role of IL-6. Multiorgan failure affects around 5% of patients with COVID-19. Zhou et al [18] reported HF as a complication of COVID-19 in 23% of the patients, more often in those who died than in survivors (51.9% vs 11.7%).[18] In patients with COVID-19, ARDS may also manifest with right-sided HF associated with pulmonary hypertension.[15] Hu et al [19] reported a case of acute HF in the course of fulminant myocarditis in a 37-year-old man without comorbidities, who presented with elevated levels of high-sensitivity troponin T and NT-proBNP and reduced left ventricular ejection fraction (27%). Clinical and echocardiographic improvement as well as a reduction in the levels of inflammatory markers were achieved with methylprednisolone and immunoglobulin. However, no data on long-term follow-up of this patient have been published.

The measurement of NT-proBNP and troponin levels in acute COVID-19 should be combined with the clinical, electrocardiographic, and echocardiographic (preferably point-of-care ultrasonography) assessment of the patient. Elevated high-sensitivity troponin levels in the acute stage of COVID-19 do not always indicate acute coronary syndrome (ACS).

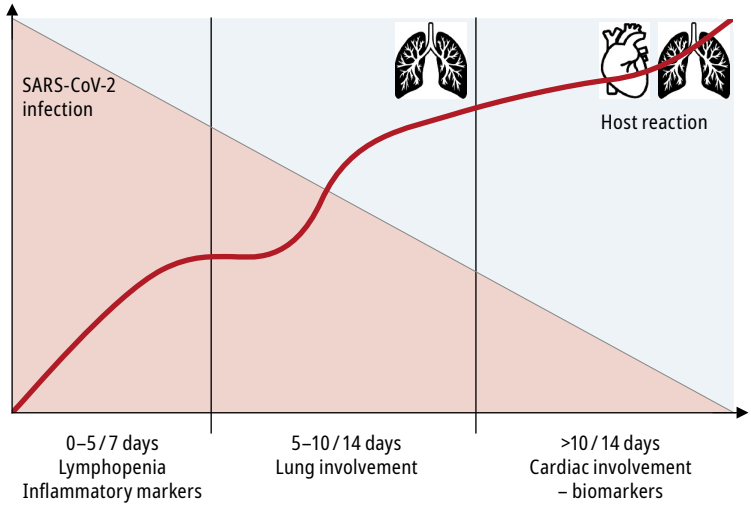

FIGURE 2 Stages of severe acute respiratory syndrome coronavirus 2 infection
Abbreviations: see FIGURE 1

De novo heart failure in coronavirus disease 2019 survivors

Long-term data in the COVID-19 population are lacking. However, it may be assumed that some survivors will develop HF by analogy to other viral diseases. Helpful diagnostic tools to identify these patients include NT-proBNP measurement and standard imaging studies such as echocardiography and cardiac magnetic resonance. Novel echocardiographic techniques, such as speckle tracking longitudinal strain imaging, may also prove useful. Heart failure may be more likely to develop in patients with cardiovascular risk factors as well as in elderly patients with comorbidities who experienced severe COVID-19 infection.

In COVID-19 survivors, cardiac assessment with or without NT-proBNP measurement is indicated, optimally combined with echocardiography. In diagnostically uncertain cases, the assessment should also include cardiac magnetic resonance imaging, if feasible. The time frame for the assessment is difficult to determine and should depend on the patient's clinical status. Currently, there are no data to support the timing and frequency of cardiac workup for HF in patients who suffered from multiorgan failure in the course of COVID-19.

The aim of cardiac assessment is to identify de novo HF in the following scenarios: 1) if the patient presents with clinical symptoms (dyspnea, reduced exercise tolerance, fatigue, signs of fluid overload) regardless of the severity of COVID-19, and 2) in all patients who recovered from stage 3 of COVID-19 (multiorgan failure), with a particular emphasis on the evaluation of the right ventricle and pulmonary artery pressure.

It is difficult to clearly determine the extent of cardiac diagnostic workup in the remaining patients with a history of SARS-CoV-2 infection.

Based on data regarding the prognosis of patients with a history of pneumococcal pneumonia (an increase in the mortality rate over the next 10 years)[20] as well as increased cardiovascular risk in those with a history of SARS, long-term cardiovascular follow-up seems to be also important in the group of patients with COVID-19.

Patients with heart failure and coronavirus disease 2019

Treatment with renin–angiotensin–aldosterone system inhibitors Angiotensin-converting enzyme inhibitors (ACEIs; or angiotensin-receptor blockers [ARBs] in case of ACEI intolerance), angiotensin receptor–neprilysin inhibitors, and mineralocorticoid receptor inhibitors constitute the cornerstone of HF therapy as drugs that block the RAA system. There is solid evidence for their beneficial effects in terms of reducing hospitalization and mortality rates in patients with HF.[21] Moreover, discontinuation of

HF therapy was shown to lead to rapid clinical deterioration (within several days or weeks) as well as an increase in long-term mortality.[22] Except angiotensin receptor–neprilysin inhibitors, renin inhibitors are the mainstay of standard therapy for hypertension or coronary artery disease. Recently, it was shown that shortly after withdrawal of some forms of valsartan from the market, there was a significant increase in the rate of emergency admissions and hospitalizations due to stroke and transient ischemic attack.[23] Moreover, the use of ACEIs or ARBs in patients with hypertension who were hospitalized due to COVID-19 was associated with a lower risk of all-cause mortality.[24]

Recently, Sommerstain and Grani[25] have put forward a hypothesis that the use of ACEIs leads to upregulation of the ACE2 expression, which may increase the individual's susceptibility to SARS-CoV-2 infection. In fact, ACE2 was identified as the functional receptor for SARS-CoV-2 by showing that ACE2-positive cells were more susceptible to viral infection. However, the infection is also possible in ACE2-negative cells, which suggests the presence of an additional route of entry.[26] Moreover, reliable data indicating that the use of ACEIs or ARBs leads to upregulation in the ACE2 expression are lacking, and the available studies are not convincing or even contradictory. While some authors confirm the link between drug administration and upregulation of the ACE2 expression,[27] others do not report such an association.[28] In addition, this was experimental research using animal or cellular models and it assessed the mRNA expression, which does not always translate to protein expression and the functionality of the receptor.

No correlation between the level of the ACE2 expression and the severity of infection was reported. Another important consideration is that the gene encoding ACE2 is located on the X chromosome, which means that men have 1 copy whereas women have 2 copies of the encoding gene. However, this was not shown to correlate with an increased incidence of COVID-19 among women. Finally, it is important to note that the ACE2 expression decreases with age.[29]

Currently, there is an ongoing pilot trial of soluble recombinant human ACE2 (APN01) in the treatment of patients with COVID-19.[30] It is hypothesized that this therapy may use the dual function of ACE2: 1) as a virus receptor to reduce the viral load, and 2) as an RAA system regulator to reduce the deleterious effects of angiotensin II.[30]

On the other hand, it is important to consider the proven beneficial effects of RAA system inhibitors on the cellular level (FIGURE 3). These effects are also crucial in the treatment of lung diseases. Lung epithelial cells contain angiotensin II receptor type 1 (AT1) and 2 (AT2), which makes the lungs susceptible to the effects of angiotensin II and angiotensin (1–7). Available evidence indicates that the RAA system plays an important role in the pathophysiology of lung disease. Inhibition of the AT1 receptor by using ARBs leads to a reduction in the inflammatory response, proliferation, and fibrosis (by reduced stimulation of the AT1-receptor signaling pathway). The use of ACEIs leads to reduced synthesis of angiotensin II by blocking

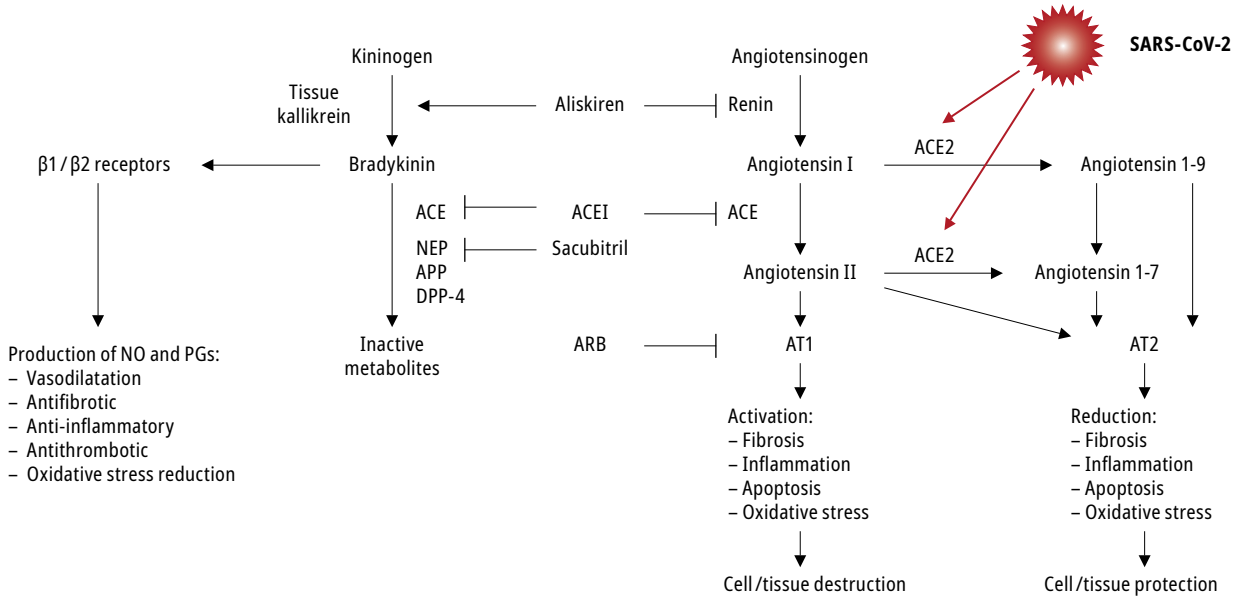

FIGURE 3 The physiological function of the renin–angiotensin–aldosterone system

Abbreviations: ACE, angiotensin-converting enzyme; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin-receptor blockers; APP, aminopeptidase P; AT1, angiotensin II receptor type 1; AT2, angiotensin II receptor type 2; DPP-4, dipeptidyl peptidase 4; NEP, neutral endopeptidase; NO nitric oxide; PG, prostaglandin; others, see FIGURE 1

the angiotensin-converting enzyme (ACE). This, similarly to ARBs, downregulates AT1 receptor activity, but additionally activates the ACE2/angiotensin (1–7) pathway, which reduces fibrosis, inflammatory response, and apoptosis. Moreover, ACE inhibition also accounts for reduced bradykinin degradation, which leads to a higher release of the endothelium-derived relaxing factor such as nitric oxide and prostanoids.[31,32]

Considering the above data and the most recent position statements of the Polish Cardiac Society as well as the European Society of Cardiology/American Heart Association/American College of Cardiology, COVID-19 patients with cardiovascular disease, including HF, should continue therapy with RAA system inhibitors or the therapy should be started as planned in newly diagnosed patients.[33]

Heart failure exacerbation in patients with coronavirus disease 2019 **Pharmacologic treatment** In patients with HF, it is particularly important to maintain the proper level of body fluids to ensure adequate organ perfusion. However, excessive fluid therapy may exacerbate hypoxemia in patients with COVID-19. Therefore, to reduce pulmonary exudate and improve oxygenation, balanced fluid therapy for adequate tissue perfusion should be provided.[34] In patients without tissue hypoperfusion, the use of conservative fluid management is associated with a shorter duration of mechanical ventilation and length of intensive care unit (ICU) stay.[34]

In the case of shock (especially septic shock), careful fluid management is recommended to avoid fluid overload. If symptoms persist despite optimal fluid therapy, the mean arterial pressure (MAP) is lower than 65 mm Hg, and no improvement of perfusion has been achieved, the use of vasopressor agents is recommended. Norepinephrine is the first-line treatment, while adrenaline and vasopressin may be additionally used to achieve optimal MAP. If symptoms of hypoperfusion and myocardial dysfunction persist despite achieving target MAP, positive inotropic therapy with dobutamine should be considered. However, due to the risk of tachycardia, dopamine should be used with caution and only in patients with bradycardia or at low risk of tachycardia. In patients older than 65 years, the MAP value of 60 to 65 mm Hg can be considered as a therapeutic target. The use of antithrombotic prophylaxis (preferably with low-molecular-weight heparin or with subcutaneous unfractionated heparin at a dose of 5000 units twice daily) is recommended in patients without contraindications. If contraindications are present, intermittent pneumatic compression should be used.[35]

Mechanical ventilation Oxygen therapy is used in 40% to 75% of patients with SARS-CoV-2 infection, while mechanical ventilation, in 6% to 10%.[1,17,36] Mechanical ventilation is recommended in patients with moderate (the ratio of partial pressure of arterial oxygen normalized to the fraction of inspired oxygen [PaO_2/FiO_2], 100–200) or severe (PaO_2/FiO_2 <100) ARDS with hypoxemia or symptoms despite oxygen supplementation.[37] Lung-protective mechanical ventilation with a target tidal volume of (usually) 6 ml/kg of predicted body weight and target plateau airway pressure of 30 cm H_2O or lower is recommended.[37] Permissive respiratory acidosis in lung-protective mechanical ventilation should be kept at a pH level of 7.25 or higher. Permissive hypoxemia with a PaO_2 of 55 to 80 mm Hg or oxygen saturation of 88% to 95% can also be considered.[37] In patients with ARDS with a PaO_2/FiO_2 of 150 or lower, prone positioning should be considered.[37] Noninvasive interventions such as noninvasive positive pressure ventilation and high-flow nasal cannula should be used with great caution due to the risk of viral transmission.[38] The value of positive end-expiratory airway pressure (PEEP) should be adjusted to the cardiovascular status (in patients with heart failure, especially in those in whom cardiac output depends on appropriate preload, higher PEEP values should be avoided or applied with caution) (FIGURE 4). For further useful information, see Supplementary material.

Extracorporeal membrane oxygenation Severe respiratory failure is reported in approximately 10% of patients with SARS-CoV-2 infection. Venovenous extracorporeal membrane oxygenation (ECMO) should be considered if any of the following criteria are met after 72 hours of mechanical ventilation: 1) PaO_2/FiO_2 <80 mm Hg (regardless of the PEEP level); 2) plateau airway pressure ≤30 mm Hg and partial pressure of carbon dioxide >55 mm Hg; 3) presence of pneumothorax, air leak exceeding one-third of tidal volume, duration longer than 48 hours; 4) circulation deterioration, norepinephrine dosage >1 μg/(kg × min); 5) cardiopulmonary resuscitation.

Early awake ECMO can also be considered in patients who have been supported by mechanical ventilation with high ventilator settings for over 7 days and who meet the necessary conditions for awake ECMO.[39]

The use of ECMO is based on the experience of single centers, and convincing data on its application in patients with COVID-19 are lacking. As SARS-CoV-2 infection causes a cytokine storm, the use of ECMO may aggravate the storm and induce further endothelial dysfunction, leading to multiorgan failure.

The use of hemoperfusion was reported in a single study. It was shown that hemoperfusion might reduce cytokine load and, at least to some extent, restore immune homeostasis.[40]

In patients with COVID-19 without severe respiratory failure yet with severe cardiovascular complications leading to cardiogenic shock,

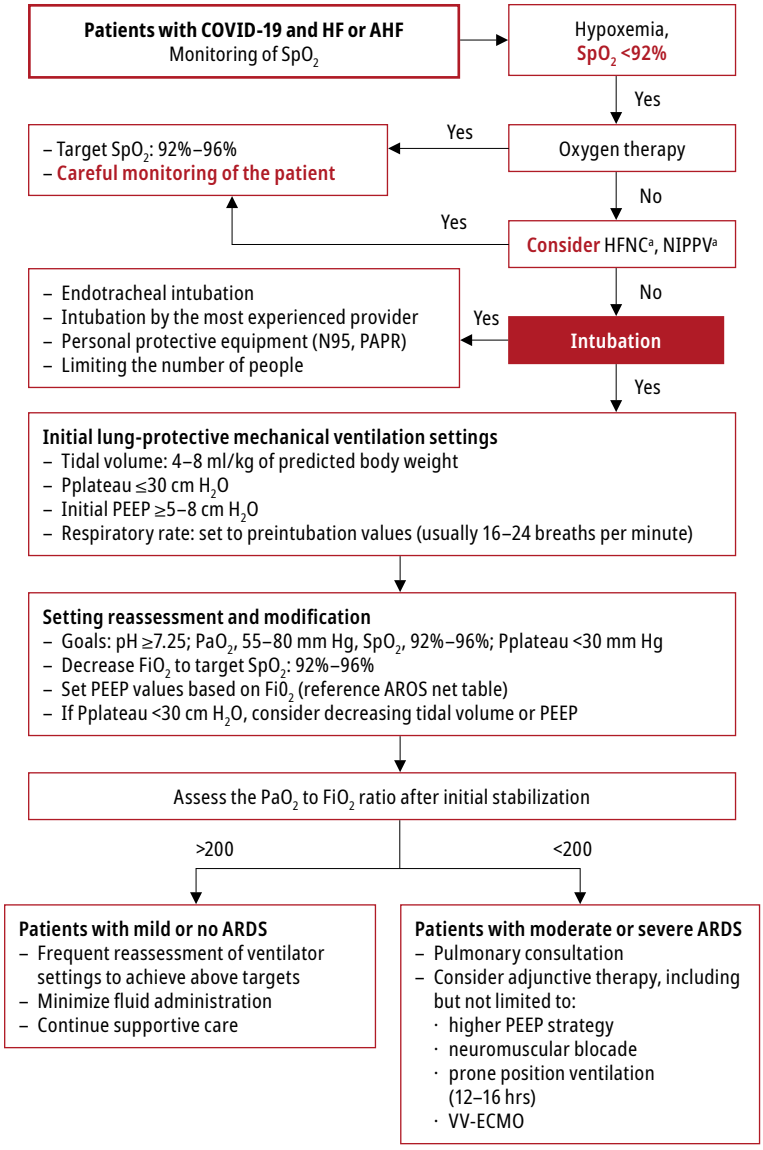

FIGURE 4 Ventilation strategy in coronavirus disease 2019. Based on Zhang et al[87]

a Use with extreme caution; deterioration or no improvement within 1 hour is an indication for intubation.

Abbreviations: AHF, acute heart failure; COVID-19, coronavirus disease 19; FiO_2, fraction of inspired oxygen; HF, heart failure; HFNC, high-flow nasal cannula; NIPPV, noninvasive positive pressure ventilation; PaO_2, partial pressure of oxygen in the blood; PAPR, powered air-purifying respirator; PEEP, positive end-expiratory pressure; Pplateau, plateau airway pressure; SpO_2, peripheral capillary oxygen saturation; VV-ECMO, venovenous extracorporeal membrane oxygenation; others, see FIGURE 1

venoarterial ECMO should be considered. For further useful information, see Supplementary material.

Arrhythmia Cardiac arrhythmia is common in patients with COVID-19 infection. In a group of 137 patients admitted to the hospital due to COVID-19, nonspecific palpitations were found in 7.3% of cases.[41] In another study, in hospitalized patients with COVID-19, arrhythmia was reported in 16.7%, and it was more common among patients staying in the ICU than outside the ICU (44.4% vs 6.9%).[10] However, no data on the types of arrhythmia have been published so far. The frequent occurrence of arrhythmia can be partly attributed to metabolic disorders, myocardial hypoxia, and inflammatory processes in the course of viral infection in patients with and without a history of cardiovascular disease. New-onset malignant tachyarrhythmia in patients with elevated troponin levels should raise a suspicion of underlying myocarditis.[16,42] Another issue that raises concern is the possible iatrogenic damage to the heart caused by drug therapy for COVID-19, especially when antiviral drugs,[10] chloroquine (CQ), or azithromycin are used (see the Treatment of coronavirus disease 2019 section).

It is extremely important to monitor electrocardiographic and electrolyte disorders (hypokalemia and hypomagnesemia may increase the risk of QTc prolongation and torsade de pointes) in patients treated for COVID-19.

The Working Group on Heart Rhythm of the Polish Cardiac Society has published an announcement on their website regarding the check-up of cardiac implantable electronic devices (pacemakers, cardiac resynchronization therapy pacemakers, implantable cardioverter-defibrillators, and cardiac resynchronization therapy defibrillators) during the COVID-19 epidemic in the general population, individuals under quarantine, and persons with suspected or confirmed infection (http://www.rytmserca.ptkardio.pl/resources/data/forms/aktualnosci/188/tryb_i_sposob_przeprowadzania_kontroli_elektronicznych_urzadzen_wszczepialnych_cied_w_okresie_epidemii_covid19.pdf).

Acute coronary syndrome as the cause of heart failure exacerbation Severe acute respiratory syndrome coronavirus 2 can cause ACS among other cardiovascular complications, but most of the available data come from observations of real-world populations treated for the infection and have not been confirmed by scientific evidence.[43,44] In a study including 75 hospitalized patients diagnosed with COVID-19, acute myocardial infarction accounted for 2 deaths among 5 fatal cases.[43]

Patients with ACS and SARS-CoV-2 infection often have poor prognosis. This is because patients with ACS develop myocardial ischemia or necrosis, which further reduces the functional reserve of the heart. Therefore, patients with SARS-CoV-2 infection are more likely to develop HF, which leads to a sudden deterioration of the clinical status. In the Wuhan patient population, a history of ACS was associated with a more severe disease course and high mortality rates. In patients with HF of ischemic etiology, SARS-CoV-2 infection may be a risk factor for rapid clinical deterioration, severe disease course, and death.[45] Another reason is the possible delay in elective invasive procedures, which may directly affect the patient's prognosis.

An algorithm has been developed for the management of patients with ST-segment elevation myocardial infarction, who require prompt reperfusion treatment, in the era of the coronavirus pandemic. In order not to delay reperfusion, the algorithm also includes fibrinolytic therapy.[46]

The principles of management in patients with ACS can be found on the website of the Association of Cardiovascular Interventions of the Polish Cardiac Society (Supplementary material).

The role of selected biomarkers There is ongoing research and discussion regarding the importance of assessing the markers of myocardial injury, inflammation, and thrombosis in patients with SARS-CoV-2 infection with a history of cardiovascular disease. The significance of myocardial injury, defined as cardiac troponin levels above the 99th percentile of the upper reference limit, independently of new electrocardiographic and echocardiographic abnormalities, in patients with SARS-CoV-2 infection has been emphasized. In a study by Shi et al,[17] increased levels of the cardiac marker, troponin, were reported in 19.7% of hospitalized SARS-CoV-2-positive patients.[17] These patients had a significantly higher in-hospital mortality compared with those without cardiac injury (51.2% vs 4.5%). Moreover, a positive correlation was observed between the levels of high-sensitivity troponin I and mortality.[17] Of note, patients with elevated troponin levels were older and more often had cardiovascular comorbidities than those without cardiac injury (hypertension, 59.8% vs 23.4%; diabetes, 24.4% vs 12%; ischemic heart disease, 29.3% vs 6%; cerebrovascular disease, 15.9% vs 2.7%; and HF, 14.6% vs 1.5%).[17] Guo et al[9] reported an association between troponin levels and the prognosis of patients with cardiovascular disease. Increased levels of high-sensitivity troponin T were correlated with higher mortality compared with the group with normal troponin levels (69.4% vs 13.3%). Moreover, normal troponin levels were associated with better prognosis in patients without cardiovascular disease (mortality rate, 7.6%).[9] Zhou et al [18] observed 2 patterns of troponin dynamics. In the most common clinical presentation with pulmonary involvement, elevated troponin levels at baseline that further increased throughout the clinical course were associated with a higher risk of death compared with patients with elevated yet stable troponin levels.[18] In patients with dominant cardiac involvement (much less common), troponin concentrations, which were significantly increased at baseline, decreased after cardiovascular support (including ECMO), which correlated with clinical improvement. This may suggest SARS-CoV-2-induced myocarditis.[19,47]

An important consideration in patients undergoing diagnostic workup for COVID-19 is that the increase in troponin concentrations is not always due to ischemic myocardial injury, which indicates the need for an individualized approach to management. In each individual patient, the results of biochemical tests are the net effect of the following: 1) the status and functional reserve of the organs at baseline; 2) severity of the systemic inflammatory response to infection; 3) the impact of the virus itself on various organs; 4) the consequences of multiorgan dysfunction due to virus activity and systemic inflammatory response.

The most frequent laboratory abnormalities in the course of COVID-19 are summarized in TABLE 1. These abnormalities indicate that, apart from progressive respiratory failure, the most common causes of unsuccessful therapy are acute HF in the course of ACS, fulminant myocarditis, Takotsubo syndrome, acute kidney and liver failure, and sepsis. Coagulation disorders are also associated with severe disease course.

The most common biochemical abnormalities indicate an uncontrolled severe inflammatory response with a cytokine storm, with increased blood levels of interleukins (IL-1 and IL-6), granulocyte colony-stimulating factor, interferon γ, tumor necrosis factor α, monocyte chemotactic protein 1, and others.[11] The cytokine storm is considered to be the major cause of multiorgan failure, secondary bone marrow suppression, and additional bacterial superinfections responsible for sepsis. On laboratory testing, this manifests as hypoalbuminemia as well as increased ferritin and procalcitonin levels. Cytokine storm is diagnosed in 3% to 4% of patients with viral sepsis and is associated with unfavorable prognosis. A useful tool for predicting cytokine storm is HScore, which has a sensitivity of 93% and specificity of 87%.[48] It can be calculated using an online calculator (http://saintantoine.aphp.fr/score/).

The role of echocardiography Echocardiography has a significant role in patients with HF and those with a complicated course of COVID-19. It helps determine the cause of dyspnea (respiratory failure or HF) and, in combination with clinical data, guides therapeutic decision-making. It is especially important in patients with concurrent pneumonia and myocarditis caused by SARS-CoV-2, as it allows for identification of patients at highest risk.

The examination should be performed at bedside and over the shortest possible time, without recording parameters that do not affect therapeutic decisions but including those that reflect basic cardiac function (ventricular size and contractility, hemodynamically significant valvular defects, pericardial effusion, inferior vena cava width, and others). Personal protective equipment should be used. If possible, the examination should be performed by a team of treating

TABLE 1 The most frequent laboratory abnormalities in patients with coronavirus disease 2019

Abnormality	Suspected cause	Relationship with more severe clinical course, need for intensive care unit stay, or prognosis of death (references)
Lymphocytes ↓	Inflammatory activation / cytokine storm	Wang et al,[10] Zhang et al,[88] Chen et al,[89] Xu et al,[90] Liu et al,[91] Wang et al,[92] Chen et al,[93] Chen et al,[94] + meta-analysis (P <0.001) by Rodriguez-Morales et al[95]
Albumin ↓		Meta-analysis (P <0.001) by Rodriguez-Morales et al[95]
Ferritin ↑		Chen et al[89]
CRP ↑		Meta-analysis (P <0.001) by Rodriguez-Morales et al[95]
White blood cells ↓		Meta-analysis (P <0.001) by Rodriguez-Morales et al[95]
Red blood cells ↓		Chen et al,[89] Chen et al[93]
Urinary protein ↑, red blood cells ↑		Li et al,[96] Cheng et al[97]
White blood cells ↑	Secondary bacterial infection	Wang et al,[10] Zhang et al,[88] Chen et al,[89] Xu et al,[90] Liu et al,[91] Wang et al,[92] Chen et al,[93] Chen et al,[94] + meta-analysis (P <0.001) by Rodriguez-Morales et al[95]
Neutrophils ↑		Chen et al,[89] Liu et al,[91] Wang et al[92]
Procalcitonin ↑		Wang et al,[10] Zhang et al,[88] Chen et al,[89] Xu et al,[90] Liu et al,[91] Wang et al[92]
LDH ↑, ALT ↑, AST ↑, bilirubin ↑	Secondary liver damage – multiorgan failure	Meta-analysis of 2 studies (AST, P = 0.427; ALT, P = 0.186; bilirubin, P = 0.004); meta-analysis of 3 studies (AST, P = 0.427); meta-analysis of 5 studies (LDH, P <0.001) by Rodriguez-Morales et al[95]
Creatinine ↑, glomerular filtration rate ↓, urea ↑	Secondary kidney damage – multiorgan failure	Creatinine and glomerular filtration rate (Chen et al,[89] Li et al,[96] Cheng et al[97]) + meta-analysis by Rodriguez-Morales et al[95] (P = 0.328), urea (Li et al,[96] Cheng et al[97])
Potassium ↓	RAAS activation	Chen et al[98]
Troponin ↑	Myocardial injury	Meta-analysis by Lippi et al[99]
NT-proBNP ↑	Increased myocardial wall tension	Shi et al[17]
D-dimer ↑	Inflammatory activation / cytokine storm	Zhang et al,[88] Chen et al,[89] Wang et al[92]
Prothrombin time ↑	Systemic coagulopathy / DIC	Shi et al[17]
Platelet count ↓		Meta-analysis by Lippi et al[100]

↑ – Increase
↓ – Decrease

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; DIC, disseminated intravascular coagulation; NT-proBNP, N-terminal fragment of the prohormone brain natriuretic peptide; RAAS, renin–angiotensin–aldosterone system; others, see FIGURE 1

physicians. Portable devices are preferable, dedicated for use in the infection zone, easy to disinfect, and enabling archiving and consulting of images.[10,15,19,39,49-52]

The examination can be extended to include pulmonary and pleural ultrasound, and, if indicated, abdominal ultrasound, to take full advantage of ultrasound capabilities and avoid additional exposure of the staff. The severity of lesions in the lung tissue can be assessed based on the presence and number of B-line artifacts (they may also occur in HF), as well as the presence of a thickened or irregular pleural line and consolidated lung tissue.[53-55] Fluid in the serous cavities is not a typical finding in patients with COVID-19.

Echocardiography should be limited to hospitalized patients with suspected cardiac causes of clinical deterioration. It is not recommended to perform echocardiography as a routine examination in all patients with COVID-19 or to perform repeat echocardiography without clear indications resulting from clinical deterioration.

Echocardiography can also be used to monitor fluid supply in patients with shock or during ECMO. Transesophageal echocardiography is an aerosol-generating procedure and requires personal protective equipment, similarly to, for example, intubation or bronchoscopy. Therefore, this type of echocardiography should be used only if absolutely necessary.

In the era of the COVID-19 pandemic, there is always uncertainty about the infectious status of the physician and the patient. Therefore, any elective tests should be postponed in patients who can be treated based on previous findings. However, the examination may be justified in the case of clinical deterioration or if there is a suspicion that echocardiographic findings will influence diagnostic and / or therapeutic decision making (also in stable patients). In such cases, the examination should be performed after collecting an epidemiological history and with the use of face masks (at least surgical) both by the patient and the physician.[49,50]

Detailed recommendations of the Working Group on Echocardiography of the Polish Cardiac Society by Gackowski et al[50] can be found at https://www.mp.pl/kardiologiapolska/issue/article/15265.

Heart transplant and mechanical circulatory support The rapid spread of the COVID-19 pandemic has changed every aspect of medicine, including the work of heart transplant (HTx) centers, in an unprecedented manner.[56] In our opinion, despite the lack of unequivocal evidence, it can be assumed that all patients with end-stage HF, history of HTx, left ventricular assist device (LVAD), or those who are awaiting HTx or LVAD implantation are at high risk of SARS-CoV-2 infection and severe disease course. Therefore, physicians are now facing 2 challenges: the management of patients after HTx or LVAD implantation and of those who are awaiting the procedure.[56]

Currently, it is recommended to minimize the number of standard visits to medical facilities, including visits to transplant centers in patients after HTx and LVAD, depending on the clinical status.[57] Elective tests, including heart biopsies, should be postponed in selected cases. Although immunocompromised patients are probably at higher risk of SARS-CoV-2 infection, prior immunosuppressive therapy should be continued.[57] According to the recent guidelines of the International Society of Heart and Lung Transplantation (ISHLT), patients after HTx or LVAD implantation with confirmed COVID-19 should be stratified depending on the severity of symptoms into groups with mild, moderate, and severe infection.[57] Patients with mild symptoms (without dyspnea or hypoxia) should be treated like any other patient. Patients with moderate (dyspnea, hypoxia requiring additional oxygen supply via the nasal cannula) and severe (need for ventilatory support due to ARDS, exacerbation of HF, or acute kidney failure) symptoms should be hospitalized, including the ICU stay. In these patients, specific therapy for COVID-19 should be started immediately, with mechanical circulatory and respiratory support as necessary (eg, ECMO), while some immunosuppressive drugs (eg, mycophenolate mofetil or azathioprine) may be temporarily discontinued (with close monitoring of possible rejection).[57]

At present, decisions regarding HTx or LVAD implantation are particularly challenging, not only due to the risk of SARS-CoV-2 infection in the donor and recipient but also because of the enormous burden of the pandemic on healthcare facilities. Although the leading societies agree that HTx surgeries should not be paused in the coronavirus era, there is ongoing discussion about the safety of the procedure in the face of possible donor and recipient infection (eg, there have been 3 updates of the Poltransplant position statement in March 2020).[56-58] Although SARS-CoV-2 transmission from the donor to recipient has not yet been confirmed, this is highly probable in the case of donor infection. For this reason, every effort must be made to achieve 2 goals at the same time: 1) a definitive exclusion of donor SARS-CoV-2 infection, and 2) exclusion of the infection in the recipient (as soon as possible, but in some urgent HTx cases, the result may be available only after the transplant).

According to the latest recommendations of Poltransplant and the ISHLT, SARS-CoV-2 infection should be excluded in every potential donor (using a real-time polymerase chain reaction [RT-PCR] test).[57,58] Similarly, although there is some controversy, Poltransplant recommends that all recipients should be tested for SARS-CoV-2, regardless of the presence of clinical symptoms. Standard RT-PCR swab testing is recommended both in the donor and the recipient.[57,58] However, given the possibility of false-negative results (especially in the case of recent infection), chest computed tomography is also recommended in donors and recipients, because it may show early signs of SARS-CoV-2 infection even before symptom onset or positive RT-PCR test results.[57,58]

The ISHLT guidance suggests that the treatment should be individualized, especially in patients with the INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) status 1–3, who were assessed as ineligible for HTx but are considered for LVAD implantation. It seems that consideration of patients with better clinical condition (higher INTERMACS status) for LVAD implantation may be temporarily postponed.[57]

As the epidemiological situation is constantly changing and clinicians gain increasing experience, the recommendations on HTx and LVAD implantation are updated on a regular basis and can be found on the Poltrnasplant website.[58]

Treatment of coronavirus disease 2019 **Efficacy and safety of new therapies** The following data on COVID-19 treatment come from the literature published until the end of April 2020,

mostly small nonrandomized clinical trials. Numerous studies are currently underway and the results has not been available yet.

Important questions are now being asked about the causal treatment of the disease and whether there are drugs that can improve outcomes in the most severe cases of COVID-19, often requiring intensive care and mechanical ventilation. So far, no evidence-based data have been published to support the efficacy of any antiviral or immunomodulatory drugs in the treatment or prevention of COVID-19 (including prophylaxis among medical personnel). Two groups of drugs seem to be effective therapeutic options in COVID-19: 1) classic antiviral drugs interfering with the spread or replication of pathogens, and 2) compounds that inhibit host inflammatory responses, particularly (and perhaps selectively) in the respiratory tract (cytokine inhibitors and specific antibodies).[59] Quinoline derivatives such as CQ and hydroxychloroquine (HCQ) seem to be particularly promising.[60]

Chloroquine was shown to exert antiviral effects against coronavirus in vitro by increasing endosomal pH (which hinders fusion between the virus and the target cell) and interfering with the glycosylation of virus cell receptors.[61] However, there are limited clinical and experimental data suggesting that CQ may provide clinical benefits in SARS-CoV-2 infection.[59,62,63] Already 15 years ago, it was reported that CQ has antiviral activity against SARS-CoV-1 in vitro.[64] Similar observations were reported for SARS-CoV-2. Wang et al[65] revealed that CQ effectively inhibit SARS-CoV-2 infection in Vero E6 cell cultures even at low micromolar concentrations (which are therefore achievable in, for example, human lung tissue).[65] Consistent results were presented by Yao et al,[66] who showed that both CQ and HCQ reduce the activity or replication of coronaviruses in in-vitro cell cultures. In addition, a small French nonrandomized open-label trial has been published recently,[67] in which HCQ with or without azithromycin was administered daily over 6 days to 20 people infected with SARS-CoV-2 (with various clinical presentations: from asymptomatic cases to overt pneumonia). At the same time, nasopharyngeal swabs were tested daily to assess viral load in the treated patients (as compared with the control group not receiving HCQ or azithromycin). The treatment increased the number of SARS-CoV-2-negative tests in the study group compared with the control group from day 3.[67] However, no data on the safety of this treatment were reported. Although this was an interesting study, it was limited by methodology and a small sample size.

Chloroquine tolerance and cardiovascular toxicity Chloroquine is an old antimalarial drug that has been widely used for decades in the therapy and prevention of this parasitic disease.[68] It has also been used as a self-medication by travelers; hence, its safety level seems to be high. The drug is also considered to be safe during pregnancy and in children, with only minor (and almost always mild to moderate) adverse effects such as headache, malaise, nausea and/or vomiting, blurred vision, itching, dizziness, concentration difficulties, and stomach symptoms.[68,69] Severe adverse effects of CQ, such as neuromyopathy, retinopathy, or idiosyncratic reactions, are rare and usually associated with long therapy duration.

The concern about the cardiovascular adverse effects of CQ seems to be related to its chemical (structural) similarity to quinidine (both substances are quinoline derivatives), an old antiarrhythmic drug that may prolong the QT interval (so called quinidine effect), which is associated with the risk of life-threatening polymorphic ventricular tachycardia (torsade de pointes).[70] However, it is likely that this well-known arrhythmogenic cardiotoxicity of quinidine should not be directly applied also to CQ.[70] The cardiovascular toxicity of oral CQ at an antimalarial dose appears to be of minor importance, because it rarely causes conduction disturbances and only slightly widens the QRS complex and prolongs the QT interval.[70]

Recommendations for physicians On March 13, 2020, the President of the Office for Registration of Medicinal Products, Medical Devices, and Biocidal Products in Poland issued a decision regarding changes in the marketing permission status for the Arechin (CQ phosphate) medicinal product. As a result, the following new therapeutic indication was added: "Supportive therapy in infections with *Betacoronavirus* such as SARS-CoV, MERS-CoV, and SARS-CoV-2" (and related drug dosing).

There are several ongoing randomized clinical trials investigating the use of CQ or HCQ in the therapy and/or prevention of COVID-19 (for more details, see the ClinicalTrials.gov website), including 1 Polish study (QUARANTINE2020 [Chloroquine as Antiviral Treatment in Coronavirus Infection 2020], NCT04331600).

Several practical issues should be discussed in this context. It is generally believed that most individuals with acquired (drug-induced) QT prolongation will never develop torsade de pointes and that numerous patients with ventricular arrhythmia have a normal QT interval shortly before the onset of arrhythmia.[71] For epidemiological and logistical reasons, even baseline electrocardiography, used to record the QT interval before treatment, will be problematic in hospitals dedicated for patients with COVID-19. Therefore, the focus should be placed on collecting an extensive medical history of potential arrhythmic events both from the patient or his or her family

(eg, palpitations with or without syncope, unexplained syncope, sudden death in the immediate family, and cases of drowning in shallow water) as well as a careful assessment of concomitant drug use to identify other substances potentially affecting the QT interval (eg, other antiarrhythmics, antibacterials, or antipsychotics). Of note, the concomitant use of CQ or HCQ with amiodarone increases the risk of severe ventricular arrhythmias. Therefore, the combined use of these drugs is contraindicated.[72]

In addition, azithromycin, which is used for respiratory infections due to SARS-CoV-2, may also induce prolonged cardiac repolarization and QT interval with the risk of serious ventricular arrhythmias.[73]

It is important to carefully monitor the CQ therapy in patients with COVID-19, including pharmacovigilance and a comprehensive assessment of the safety profile.

Novel perspectives in the treatment of coronavirus disease 2019 The concept of cytokine storm has led to research on the use of recombinant anti-IL-6 or anti-IL-6 receptor antibodies to inhibit the excessive activation of IL-6. The investigated drugs include tocilizumab, which targets the IL-6 receptor and possibly modulates the inflammatory process associated with SARS-CoV-2 infection, as well as several neutralizing monoclonal antibodies targeting the molecular mechanism of SARS-CoV and MERS-CoV.[74,75]

TMPRSS2 inhibitors block the entry of SARS-CoV-2 into the cell.[76,77] A known TMPRSS2 inhibitor on the market is camostat mesylate.

There are also ongoing trials of antiviral-specific treatment. Drugs that inhibit viral RNA synthesis include remdesivir, favipiravir, and ribavirin. Remdesivir is a new nucleotide analogue with a broad spectrum of antiviral activity against single-stranded RNA viruses, including the Ebola virus.[78-81] The drug inhibits RNA-dependent RNA polymerase, which is crucial in the replication of viral RNA in the host cell. Animal model and cell line studies suggested the efficacy of remdesivir in the selective inhibition of MERS-CoV and SARS-CoV-2 infection.[78,82] Experimental treatment with intravenous remdesivir in the first patient with COVID-19 in the United States has shown a very promising response.[83] A multicenter randomized placebo-controlled phase 3 clinical trial to determine the efficacy and safety of remdesivir in COVID-19 is currently underway.[84] A preliminary analysis of data from a randomized controlled trial involving 1063 patients, which was started on February 21, 2020, showed that hospitalized patients with advanced COVID-19 and lung involvement who received remdesivir recovered faster than similar patients receiving placebo.[85] This is the first such clinical trial in the United States to assess experimental COVID-19 treatment.

Other forms of therapy also seem promising, including nonsteroidal anti-inflammatory drugs and low-dose corticosteroids; tumor necrosis factor inhibitors; Janus kinase inhibitors, mycophenolate mofetil, tacrolimus, anti-CD20 monoclonal antibodies, and CTLA4-Ig fusion protein. However, firm evidence on the efficacy of these therapies is lacking.[86]

Vaccine research is ongoing, including several studies at an advanced stage (ClinicalTrials.gov identifiers, NCT04299724, NCT04276896, NCT04283461, NCT04334980, NCT04341389).

Conclusions The current position statement is a summary of information on patients with COVID-19 and concomitant HF or at risk of HF. We are aware that this document is not conclusive owing to a limited number of reports, coming mainly from Chinese and American centers, and also owing to the high dynamics of the pandemic. The management of patients with HF during the coronavirus pandemic should be based on maintaining current pharmacotherapy in line with applicable guidelines of the European Society of Cardiology and the Polish Cardiac Society. Indications for elective interventions (revascularization, electrotherapy, heart valve procedures, and others) should be assessed on an individual basis and according to the patient's clinical status, with a possibility of rescheduling to a later date. Considering the limited contact with the treating physician, telemedicine and self-monitoring are becoming particularly important (http://www.slabeserce.pl/). As the epidemiological situation is unpredictable and the pandemic may be long-lasting, it is necessary to change the organization of care for HF patients, particularly those at high risk, so that the care is provided in dedicated centers with measures introduced to ensure the maximum safety and minimal risk of infection.

SUPPLEMENTARY MATERIAL

The Polish version of the paper and supplementary material are available at www.mp.pl/kardiologiapolska.

ARTICLE INFORMATION

CONFLICT OF INTEREST None declared.

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